Stem cell tolerance through the use of engineered antigen-specific regulatory T cells

Grant Award Details

Stem cell tolerance through the use of engineered antigen-specific regulatory T cells

Grant Type: Transplantation Immunology

Grant Number: RM1-01703

Project Objective: The overarching objective of this project is to generate ex vivo expanded Tregs which could block alloimmune and autoimmune attack of SC derived islets in an antigen specific manner.

Investigator:

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Type:	PI

Disease Focus: Diabetes, Immune Disease

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $1,152,768

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Stem cell tolerance through the use of engineered antigen-specific regulatory T cells

Public Abstract: Type 1 Diabetes (T1D) occurs as a consequence of uncontrolled immune activation, culminating in the destruction of insulin-producing beta-cells. Efforts to prevent or reverse diabetes have been limited by the lack of safe and effective immunotherapies coupled with the inability to restore insulin producing beta-cells. We believe proper immune control to self-tissues to be a fundamental requirement for any effective therapy, whether the goal is prevention of early beta-cell loss, beta-cell regeneration at disease onset, or ultimately beta-cell replacement in cases of established T1D. To impact disease, any effective therapy must first restore a glucose-responsive insulin-producing beta-cell population. Stem cells represent one of the most promising alternative sources of insulin-producing cells. Second, a therapy must combat the persistent autoimmune attack, as well as any attack directed at foreign tissues following transplantation. The goal of this project is to bring together research efforts in these two complementary areas to fill these critical gaps. Previous studies have focused on the use of regulatory T cells (Tregs) as one key means of restoring immune tolerance in T1D. A key parameter has been the importance of antigen specificity in directing the tissue-protective functions of Tregs. In the prevention setting, antigen-specific Tregs were at least 100-fold more effective in controlling diabetes when compared to Tregs with diverse receptors. Importantly, treatment with antigen-specific Tregs is capable of reversing diabetes in the non-obese diabetic (NOD) mouse model of T1D. Likewise, these Tregs have also been shown to be important in preventing tissue rejection in the transplantation setting. Thus, Treg specificity determined by the T cell receptor can be exploited to selectively suppress a particular component of an ongoing immune response. The translation of this knowledge requires a robust means to generate a large number of patient-derived antigen-specific Tregs. The goal of this proposal is to test the hypothesis that the introduction of antigen-specific Tregs will be able to correct the initiating and persistent autoimmunity in T1D, as well as prevent the transplant-mediated destruction of beta-cells following stem cell transplantation. Thus, we propose to develop engineered tissue-directed human regulatory T cells capable of suppressing autoimmune and transplant-related destruction of beta-cells. To generate these cells we will deliver the specific T cell receptors (TCRs) by gene therapy delivery mechanisms to a patient's own Treg population and test their ability to suppress specific immune responses in immunodeficient mice following beta-cell replacement therapies.

Statement of Benefit to California:	Type 1 diabetes (T1D), previously referred to as Juvenile Diabetes, is a chronic condition that leads to devastating consequences for patients and places a huge financial burden on the California health care system. T1D occurs as a consequence of the systematic immune destruction of the insulin-producing beta cells in the pancreas. Once those cells are destroyed, the production of insulin is dramatically compromised and patients lose the ability to control blood sugar levels. Chronic periods of elevated blood sugar result in numerous secondary complications including heart disease, blindness, kidney failure, and abnormal nervous system function, among others. There is currently no known way to prevent T1D. According to the California Department of Public Health, there were 2.7 million Californians with diabetes in 2007, meaning that 1 out 10 adult Californians has diabetes. Of these, approximately 5-10% of patients have T1D, with the remainder consisting of patients with insulin-resistant type 2 diabetes. Of particular concern, the incidence rate of T1D has been increasing, particularly in children 5 years old and under. T1D is the second most common chronic disease in children, second only to asthma. Consequently T1D, and improved therapeutic approaches for this disease, are issues of great importance to the people of California. Intensive insulin therapy is the only current treatment for T1D. While effective at reducing blood sugar levels in the short term, insulin therapy does not address the underlying autoimmune attack which leads to T1D. Our studies will explore the potential use of human embryonic stem cells to restore insulin-producing cells. In addition, we are exploring ways to genetically modify (through the use of gene therapy) a population of regulatory cells (Tregs) within the immune system to stop the autoimmune attack that initiates T1D. We expect that these modified Tregs will not only stop the autoimmune process, but will also protect against the immune attack which normally arises against the transplanted tissues and any stem cell-derived tissues. We hope to eventually use these procedures to treat patients with T1D. If successful, our results may allow patients with T1D to discontinue, or greatly reduce the amount of insulin they must currently take to maintain normal blood sugar levels. This approach will directly benefit those with T1D, as well as the general population by reducing the health care burden associated with the care of this chronic disease.

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